nature reviews cardiology

https://doi.org/10.1038/s41569-024-01064-4

Review article

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Mechanisms and treatment of pulmonary arterial hypertension

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Abstract

Substantial progress has been made in the management of pulmonary arterial hypertension (PAH) in the past 25 years, but the disease remains life-limiting. Established therapies for PAH are mostly limited to symptomatic relief by correcting the imbalance of vasoactive factors. The tyrosine kinase inhibitor imatinib, the first predominantly non-vasodilatory drug to be tested in patients with PAH, improved exercise capacity and pulmonary haemodynamics compared with placebo but at the expense of adverse events such as subdural haematoma. Given that administration by inhalation might reduce the risk of systemic adverse effects, inhaled formulations of tyrosine kinase inhibitors are currently in clinical development. Other novel therapeutic approaches for PAH include suppression of activin receptor type IIA signalling with sotatercept, which has shown substantial efficacy in clinical trials and was approved for use in the USA in 2024, but the long-term safety of the drug remains unclear. Future advances in the management of PAH will focus on right ventricular function and involve deep phenotyping and the development of a personalized medicine approach. In this Review, we summarize the mechanisms underlying PAH, provide an overview of available PAH therapies and their limitations, describe the development of newer, predominantly non-vasodilatory drugs that are currently being tested in phase II or III clinical trials, and discuss future directions for PAH research.

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Key points

- Established therapies for pulmonary arterial hypertension (PAH), which has a complex vascular pathobiology characterized by cell proliferation, extracellular matrix deposition and inflammation, have predominantly vasodilatory effects.
- The tyrosine kinase inhibitors imatinib and seralutinib have predominantly anti-proliferative properties and have been reported to be efficacious in the treatment of PAH in clinical trials; administration by inhalation might address the safety concerns associated with orally administered imatinib.
- Therapy with the activin receptor type IIA ligand trap sotatercept was effective in patients with PAH in clinical trials; an ongoing extension study might address questions regarding long-term cardiac and systemic vascular safety.
- The effect of PAH therapy on load-independent right ventricular function, an important determinant of outcomes in these patients, requires further investigation.
- Individual responses to different PAH treatments might vary; deep phenotyping might help to identify biomarkers associated with drug-specific responses and support the development of a personalized medicine approach.

Introduction

Pulmonary arterial hypertension (PAH) is a life-limiting pulmonary vascular disease (PVD) characterized by pulmonary vasoconstriction and vascular remodelling[1,2]. The resulting progressive increase in pulmonary vascular resistance (PVR) challenges the right ventricle, which initially responds by increasing contractility mainly through hypertrophy to preserve right ventricular (RV)–pulmonary arterial coupling. However, this adaptative process eventually becomes less effective, resulting in RV dilatation and failure[3]. RV function is a key determinant of survival in patients with PAH[4].

PAH is a subtype of pulmonary hypertension. Pulmonary hypertension is classified based on pathophysiological mechanisms, clinical presentation, haemodynamic characteristics and therapeutic management[5]. The other main subtypes include pulmonary hypertension associated with left-sided heart disease (group 2), lung diseases and/or hypoxia (group 3), pulmonary artery obstruction (group 4), or unclear or multifactorial mechanisms (group 5)[5]. A key symptom of pulmonary hypertension is dyspnoea on progressively mild exertion. Other symptoms and signs, such as fatigue, rapid exhaustion, palpitations, exertional (pre)syncope, cyanosis and an accentuated pulmonary component of the second heart sound, can raise suspicion of pulmonary hypertension. Tests for pulmonary hypertension include electrocardiography assessment, chest X-ray, cardiopulmonary exercise testing and CT. Echocardiography is an important non-invasive tool to determine the probability of pulmonary hypertension, and patients with an intermediate or high probability of the disease should be referred to a specialized pulmonary hypertension centre for comprehensive workup, including diagnostic pulmonary haemodynamic assessment by right heart catheterization.

PAH is a form of pre-capillary pulmonary hypertension that is currently defined as a mean pulmonary arterial pressure (mPAP) of >20 mmHg, with a pulmonary arterial wedge pressure of ≤15 mmHg and PVR of >2 Wood units[5]. Treatment of PAH is guided by the specific subtype of the disease, the presence or absence of vasoreactivity and cardiopulmonary comorbidities, and assessment of risk (based on prognostic determinants, including haemodynamic and imaging parameters, levels of brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiopulmonary exercise test parameters, exercise capacity, functional class, syncope, rate of progression of symptoms and clinical manifestations, and signs of right-sided heart failure), with a goal of achieving and maintaining a low-risk status[5]. Of note, pivotal trials of PAH therapies have been conducted in patients with mPAP ≥25 mmHg and PVR >3 Wood units; the efficacy of these therapies for patients with mPAP <25 mmHg and PVR <3 Wood units has not yet been established[5]. Patients with PAH might also have features of other forms of pulmonary hypertension that PAH therapies have not yet been approved to treat. For example, atypical idiopathic PAH has been identified as an intermediate form of pulmonary hypertension that shares features of both typical idiopathic PAH (group 1) and pulmonary hypertension due to heart failure with preserved ejection fraction (group 2)[6]. Idiopathic PAH with a lung phenotype resembling group 3 pulmonary hypertension has also been described[7].

Drug development for pulmonary hypertension is undergoing a dramatic shift, with the advent of novel drugs such as tyrosine kinase inhibitors and activin receptor ligand traps (including sotatercept, which was approved by the FDA in March 2024 for the treatment of PAH in adults[8]). In this Review, we summarize the mechanisms underlying PAH, provide an overview of established PAH therapies and their limitations, describe the development of (predominantly non-vasodilatory) drugs that are undergoing assessment in phase II or phase III clinical trials, and discuss future directions for PAH research.

Pathophysiology

PAH has a complex pathophysiology, with multiple mechanisms (genetic, epigenetic and environmental) that together result in pulmonary vasoconstriction and vascular remodelling[2] (Fig. 1).

Genetic drivers

Variants in bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor-β (TGFβ) superfamily, are present in 70–80% of families with PAH and 10–20% of patients with idiopathic PAH[9]. The loss of BMPR2 promotes endothelial dysfunction[10,11], endothelial-to-mesenchymal transition[12] and pulmonary arterial smooth muscle cell hyperproliferation[13]. Variants in the BMPR2 co-receptors activin receptor-like kinase 1 (ALK1; also known as serine/threonine protein kinase receptor R3) and endoglin have been associated with PAH and with hereditary haemorrhagic telangiectasia, which can co-segregate with PAH[14–16]. PAH is also associated with variants in the BMPR2 ligand BMP9 (which acts as a vascular quiescence factor), the downstream effector SMAD8 (encoded by *SMAD9* and involved in microRNA regulation), caveolin 1 (involved in the co-localization of BMPRs) and the potassium channel subfamily K member 3 (KCNK3; which influences vascular tone)[9,17].

Epigenetic drivers

An upregulation in the expression of DNA methyltransferase (DNMT; including DNMT1 and DNMT3b) has been implicated in the development of PAH through downregulation of the expression of vasoprotective genes such as the gene encoding superoxide dismutase 2 (ref. 18).

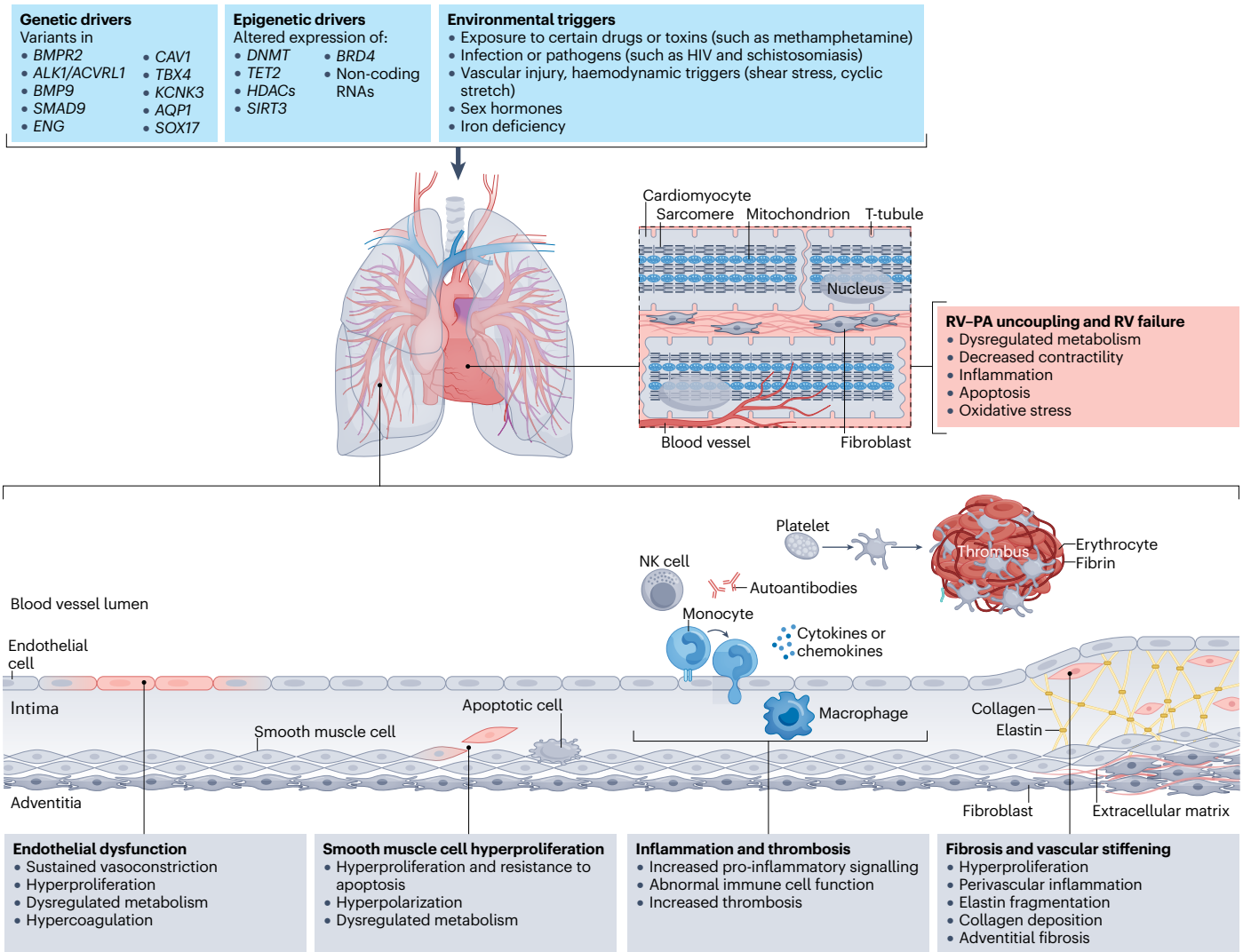

Fig. 1 | Pathomechanisms of pulmonary arterial hypertension. Genetic, epigenetic and environmental factors (blue text boxes) contribute to the development of pulmonary arterial hypertension by affecting both the pulmonary vasculature (grey text boxes) and right ventricular (RV) function (pink text box). Endothelial dysfunction leads to vasoconstriction and vascular remodelling (hyperproliferation and fibrosis) in the pulmonary vessels, causing an increase in RV afterload. The adaptation of RV contractility to the increase in afterload (RV–pulmonary arterial (PA) coupling) is a key determinant of outcome. Eventually, the adaptive process is exhausted and RV dilatation and failure ensue. NK, natural killer.

Hypermethylation of the *BMPR2* promoter to inhibit *BMPR2* expression has also been reported in patients with PAH[19]. Interestingly, variants in *DNMT3* and *TET2*, which encode proteins that methylate and demethylate DNA, respectively, have been associated with PAH[20,21]. The mechanisms underlying how variants in *DNMT* might cause PAH are unclear but an increase in inflammation (as seen with variants in *TET2*) has been suggested as a potential pathway[22].

Histone deacetylases (HDACs) regulate the acetylation status and activity of cytoplasmic proteins, suppress transcription by causing chromatin compaction, and have been associated with proliferative and inflammatory phenotypes linked to vascular remodelling[23]. HDAC1, HDAC5 and HDAC6 have been shown to be upregulated in the lungs of patients with PAH[24,25]. PAH has also been associated with reduced expression and activity of sirtuin 3, a predominantly mitochondrial NAD-dependent deacetylase[26], and with increased expression of bromodomain-containing protein 4 (BRD4), a reader of acetyl moieties that promotes the expression of oncogenic and pro-inflammatory factors[27].

MicroRNAs have also been implicated in the pathogenesis of PAH[28]. For example, miR-138-5p was found to be upregulated in patients with PAH and a rat model of pulmonary hypertension, and its inhibition in the rat model restored KCNK3 expression, improved pulmonary haemodynamics and decreased pulmonary vascular remodelling[29].

Environmental factors

Pharmacological triggers. PAH can be triggered by exposure to certain drugs or toxins. Specific appetite suppressants (such as fenfluramine derivatives), toxic rapeseed oil, methamphetamine,

α-interferons and β-interferons, and certain tyrosine kinase inhibitors (including dasatinib) have been associated with the development of pulmonary hypertension[5]. The link between methamphetamine use and PAH is of particular concern given that 2 million people in the USA were reported to have used methamphetamine in 2019 (ref. 30) and the increasing usage rates observed in Europe and Asia[31]. Methamphetamine shares pharmacological similarities with the serotonin-releasing agent fenfluramine[32,33]. Methamphetamine triggers the release of noradrenaline and serotonin[34], both of which promote smooth muscle cell proliferation and contraction[35–38]. The association between dasatinib and PAH is also noteworthy and seemingly paradoxical given that other tyrosine kinase inhibitors, such as imatinib, are being investigated as potential PAH therapies. This difference in their effects might be attributable to the broader spectrum of kinases targeted by dasatinib compared with imatinib[39].

Infection and inflammation. Human immunodeficiency virus (HIV) and schistosomiasis infections are associated with the development of PAH[40,41]. Although HIV does not infect pulmonary vascular or endothelial cells[42,43], the expression of HIV-associated proteins, such as envelope glycoprotein gp120 and Tat (which stimulate the release of endothelin 1 and reactive oxygen species, respectively[44,45]), might contribute to endothelial dysfunction. Inflammatory pathways stimulated by HIV or by other infections that occur frequently in patients with HIV might also contribute to the development of PAH[40]. Schistosomiasis, an acute or chronic infection caused by parasitic tapeworms, is one of the most common causes of PAH in tropical regions, but the underlying mechanisms are largely unknown. Schistosome eggs deposited in the lungs are believed to elicit an immune response, which in turn promotes pulmonary vascular inflammation and remodelling[41]. Of note, inflammation is a common feature of pulmonary hypertension[46]. Inflammatory connective tissue diseases, such as systemic sclerosis, are known to be associated with PAH (albeit to varying degrees[47]). Evidence suggests that altered haemodynamic forces cause lung endothelial dysfunction[48], leading to adherence and infiltration of immune cells[48,49] and the release of inflammatory mediators such as tumour necrosis factor and IL-6 (ref. 50). The resulting perivascular inflammation has been suggested to promote vascular remodelling and the progression of pulmonary hypertension in a cyclical manner[46,51].

Sex-specific disparities. Women are more likely than men to develop PAH but women with PAH have better outcomes than men with PAH[52]. The physiological mechanisms underlying this so-called 'oestrogen paradox' are complex and incompletely understood, but studies from the past 15 years suggest the involvement of multiple sex-specific hormones, receptors and metabolites[53–59] with possible time-dependent and compartment-specific effects[52]. Interestingly, dehydroepiandrosterone (DHEA) sulfate, a precursor for oestrogen and testosterone synthesis, seems to have a protective role given that circulating levels of DHEA are lower in patients with PAH than in controls[54,55,60] and are inversely associated with the severity of PAH[54,60].

Iron deficiency. Iron deficiency, one of the most common nutritional deficiencies in the world[61], has been associated with poor clinical outcomes in patients with PAH[62–65]. According to current PAH treatment guidelines, correction of iron status is recommended in patients with iron-deficiency anaemia, and iron repletion can also be considered for iron deficiency in the absence of anaemia[5].

Mechanical factors

Wall shear stress can influence intracellular energetics, cytoskeletal structure and vascular tone[66]. A decrease in wall shear stress has been observed in the main pulmonary arteries of patients with pulmonary hypertension compared with controls with mPAP <25 mmHg[67] and is associated with imbalanced production of vasoactive factors by endothelial cells[68], extracellular matrix remodelling[69,70], inflammation[69], and smooth muscle cell proliferation and migration[71]. An elevation in pulmonary pressure can also increase cyclic stretch[66], which has been shown to promote the proliferation of pulmonary arterial endothelial and smooth muscle cells[72], stimulate extracellular matrix remodelling[73], and increase the stiffness of endothelial cells[74,75]. An increase in pulmonary pressure can also cause a mechanical breakdown of capillary membranes, leading to increased permeability and remodelling[66].

Molecular and cellular changes in the lungs

Endothelial dysfunction leads to an increased release of endothelin 1 and blunts the release of nitric oxide and prostacyclin, pathways that affect vasoconstriction and cell proliferation and are targeted by established PAH therapies[5,76]. Endothelin 1 promotes smooth muscle cell depolarization and vasoconstriction by inhibiting potassium channel currents and upregulating calcium channel and transient receptor potential canonical channel currents through the phospholipase C–protein kinase C pathway[77–79]. The nitric oxide pathway promotes vasorelaxation by activating potassium channel currents and inhibiting store-operated calcium entry via protein kinase G[80–83], whereas the prostacyclin pathway activates potassium channel currents via protein kinase A[84].

Endothelial cells in patients with PAH also show increased expression of adhesion molecules (including E-selectin, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1)[85], recruitment of inflammatory cells[85], increased oxidative stress[86], reduced anticoagulatory properties[87], and acquisition of a pro-proliferative and antiapoptotic phenotype[88]. These changes promote vascular remodelling[76], which is characterized by the progressive accumulation of pulmonary arterial smooth muscle cells and adventitial fibroblasts that have a marked pro-inflammatory phenotype[89].

The lungs of patients with PAH also show increased expression of growth factors, including vascular endothelial growth factor[90] and platelet-derived growth factor (PDGF)[91,92], and altered levels of inflammatory mediators (increased IL-6 (ref. 93) and IL-1 receptor type 1 (ref. 94) and decreased peroxisome proliferator-activated receptor-γ[95]). Pulmonary vascular cells in patients with PAH also show altered activity of transcription factors (including nuclear factor of activated T cells and nuclear factor-κB)[2], dysregulated DNA damage response pathways (such as increased expression and activation of the DNA repair protein poly(ADP-ribose) polymerase 1)[88] and a shift towards glycolytic metabolism (the Warburg effect) and fatty acid oxidation, similar to cancer cells, resulting in reduced sensitivity to cell death mediators[88].

Molecular mechanisms of RV dysfunction

Patients with PAH who are carriers of a genetic variant in *BMPR2* have more severely compromised RV function than non-carriers with PAH with a similar afterload, suggesting a genetic contribution to RV failure[96,97]. Epigenetic alterations might also be involved in the transition from compensated RV hypertrophy to decompensated RV failure. An upregulation in DNMT3A and DNMT3B has been reported in decompensated versus compensated RV hypertrophy; this upregulation led to the hypermethylation of the miR-126 promoter and consequently

decreased the expression of miR-126, leading to reduced angiogenesis and vascular density in the right ventricle[98]. Inhibition of hypoxia-inducible factor 1α might also contribute to reduced angiogenesis in decompensated RV failure[99].

Sex hormones might also affect RV function. Post-menopausal hormone therapy use, DHEA plasma levels and single-nucleotide variants that modulate oestrogen activity have all been associated with RV structural remodelling or function[54,58,59]. In animal models of pulmonary hypertension, oestrogen seems to protect against RV dysfunction[100–103], but whether this protection is a direct effect on RV cells or an indirect effect of reducing RV afterload is unknown[104].

RV dysfunction in the setting of pulmonary hypertension might also be influenced by cytoskeletal alterations. A study using a rat model of pulmonary hypertension showed abnormal T-tubule architecture and decreased junctophilin 2 expression in RV cardiomyocytes[105]. Patients with PAH were found to have increased RV diastolic stiffness that was linked to sarcomeric stiffening and reduced titin phosphorylation in RV cardiomyocytes[106]. Furthermore, increased passive stiffness in RV cardiomyocytes has been observed in both patients with idiopathic PAH and patients with systemic sclerosis-associated PAH compared with individuals without PAH, but maximal calcium-activated force was elevated in those with idiopathic PAH and reduced in those with systemic sclerosis-associated PAH, consistent with the worse clinical outcomes observed in the latter group[107]. The maximal calcium-activated force correlated directly with RV contractility and contractile reserve.

The role of inflammation in the pathogenesis of pulmonary hypertension-associated RV dysfunction is not well defined[108]. Animal models of RV pressure overload show an upregulation in inflammatory mediators, including various chemokines (such as CC-motif chemokine ligand 2 (CCL2), CCL3, CCL4, CCL6, CXC-motif chemokine ligand 1 (CXCL1), CXCL2, CXCL3, CXCL9, CXCL10 and CXCL16), CC-motif chemokine receptor 1, CXC-motif chemokine receptor 4, IL-1β, IL-6 and tumour necrosis factor[109]. RV dysfunction in patients with PAH has also been linked to inflammatory processes[109]. For example, high circulating levels of IL-6, CXCL10, CXCL12 and CXCL16 were associated with RV dysfunction in patients with PAH[110,111]. Furthermore, patients with PAH and RV decompensation showed increased numbers of $CD68^+$ macrophages in RV tissue compared with controls with cardiomyopathies other than PAH[112]. Chronic inflammation in the setting of pressure overload RV dysfunction has been suggested to contribute to RV fibrosis by promoting cardiac fibroblast proliferation and activation and increasing collagen deposition[113].

Finally, metabolic processes are altered in the right ventricle of patients with PAH. RV failure is characterized by an increase in glycolysis[114,115] and a reduction in fatty acid oxidation[116–118]. The shift to glycolysis is mediated by pyruvate dehydrogenase kinase and is associated with decreased RV contractility and prolongation of the RV monophasic action potential duration and QT(c) interval due to decreased expression of repolarizing voltage-gated potassium channels[115]. The accompanying reduction in fatty acid oxidation involves the downregulation of enzymes in lipid metabolism pathways (such as ARV1 homologue fatty acid homeostasis modulator, lipoic acid synthetase, phosphatidylinositol glycan anchor biosynthesis class K and palmitoyl–protein thioesterase 1) and might lead to toxic lipid accumulation[116,117,119]. Levels of ceramide, a lipotoxic and pro-apoptotic triglyceride metabolite, are increased in RV tissue from patients with PAH compared with controls[116].

Established PAH therapies

Targeted PAH therapies

Therapies targeting the prostacyclin, endothelin or nitric oxide pathways are recommended for patients with PAH who do not show an immediate haemodynamic improvement in response to an acute vasodilator challenge or who do not have a sustained response to high-dose calcium channel blocker therapy[5]. The primary outcomes of the pivotal trials of targeted PAH therapies approved in the USA or Europe are summarized below.

Prostacyclin analogues. The prostacyclin analogue epoprostenol was evaluated in a randomized, controlled, open-label, 12-week study in patients with PAH (NYHA class III–IV)[120]. In this pivotal study, intravenous epoprostenol improved both exercise capacity (6-min walk distance (6MWD)) and haemodynamic measurements compared with conventional therapy. This study remains the only PAH trial to date to show increased survival with the new drug being tested compared with standard therapy. Of note, however, the conventional background therapy in this study (consisting of anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides and supplemental oxygen) differed from that of subsequent studies (in which patients may have received other established PAH treatments as background therapy) and the patients all had advanced disease. Subsequently approved prostacyclin analogues were designed to have a more favourable safety profile and more convenient routes of administration. Pivotal trials assessing subcutaneous treprostinil[121], inhaled iloprost[122], inhaled treprostinil[123] and oral treprostinil[124] demonstrated an improvement in 6MWD over 12 weeks compared with placebo (Table 1). Intravenous treprostinil showed bioequivalence to subcutaneous treprostinil in healthy volunteers[125] and might be considered when subcutaneous treprostinil infusion is not tolerated[126]. Furthermore, the oral prostacyclin receptor agonist selexipag reduced the incidence of a composite of death and complications arising from PAH compared with placebo, irrespective of background therapy[127]. The majority of the primary end point events (81.9%) were hospitalizations or disease progression.

Endothelin receptor antagonists. Similarly, the pivotal trials assessing the oral endothelin receptor antagonists (ERAs) bosentan[128] and ambrisentan[129] demonstrated an improvement in 6MWD compared with placebo over 16 weeks and 12 weeks, respectively, in treatment-naive patients with PAH (Table 1). A subsequent trial assessing the ERA macitentan in patients with PAH who were already receiving up to two PAH-specific background therapies showed that the drug reduced the incidence of a composite of morbidity and mortality compared with placebo[130].

Targeting the nitric oxide pathway. Nitric oxide stimulates soluble guanylate cyclase (sGC) to generate cyclic guanosine monophosphate, which is degraded by phosphodiesterase 5 (PDE5)[5]. In treatment-naive patients with PAH, the oral PDE5 inhibitors sildenafil[131] and tadalafil[132] improved 6MWD after 12 weeks and 16 weeks of treatment, respectively, compared with placebo. Similarly, in patients with symptomatic PAH who were receiving ERAs or prostanoids or not receiving other PAH-specific treatment, the sGC stimulator riociguat improved 6MWD at 12 weeks compared with placebo[133].

Initial combination therapy

The phase III–IV AMBITION trial[134] compared the efficacy of initial ambrisentan or tadalafil monotherapy with that of initial ambrisentan

Table 1 | Completed and published phase III clinical trials in PAH

Trial (year)	Drug	Trial design	Patient cohort	Major findings	Ref.
Pivotal trials in PAH that resulted in approval of therapy in the USA or Europe					
Barst et al. (1996)	Epoprostenol, continuous IV infusion	Randomized, open-label	81 patients with idiopathic PAH	Epoprostenol treatment led to symptomatic and haemodynamic improvements and improved survival	120
Simonneau et al. (2002)	Treprostinil, continuous SC infusion	RCT	470 patients with PAH	Treprostinil improved exercise capacity, signs and symptoms of PH, and haemodynamics	121
AIR (2002)	Iloprost, aerosolized	RCT	203 treatment-naive patients with various types of PH	Treatment with iloprost improved a combined endpoint consisting of 6MWD, NYHA functional class and clinical deterioration	122
BREATHE-1 (2002)	Bosentan	RCT	213 treatment-naive patients with idiopathic PAH or CTD-PAH	Bosentan improved exercise capacity and WHO functional class and increased time to clinical worsening	128
SUPER (2005)	Sildenafil	RCT	278 treatment-naive patients with PAH	Sildenafil improved exercise capacity, WHO functional class and haemodynamics	131
ARIES-1 and ARIES-2 (2008)	Ambrisentan	RCT	202 (ARIES-1) and 192 (ARIES-2) treatment-naive patients with PAH	Ambrisentan improved exercise capacity and WHO functional class	129
PHIRST-1 (2009)	Tadalafil	RCT	405 patients with PAH (treatment-naive or receiving bosentan)	Tadalafil improved exercise capacity and quality of life measures and reduced clinical worsening	132
TRIUMPH I (2010)	Treprostinil, inhaled	RCT	235 patients with PAH receiving sildenafil or bosentan	Treprostinil improved exercise capacity and quality of life	123
FREEDOM-M (2013)	Treprostinil, oral	RCT	349 patients with PAH (not receiving other PAH therapies)	Treprostinil improved exercise capacity	124
PATENT-1 and PATENT-2 (2013)	Riociguat	RCT	443 patients with PAH (treatment-naive or receiving ERA or a non-IV prostacyclin analogue)	Riociguat improved exercise capacity and WHO functional class	133
SERAPHIN (2013)	Macitentan	RCT	742 patients with PAH (treatment-naive or receiving PDE5 inhibitor and/or an oral or inhaled prostacyclin analogue)	Macitentan reduced morbidity and mortality	130
GRIPHON (2015)	Selexipag	RCT	1,156 patients with PAH (treatment-naive or receiving ERA and/or PDE5 inhibitor)	Selexipag reduced risk of a combined end point of death or complications related to PAH	127
STELLAR (2023)	Sotatercept, SC	RCT	323 patients receiving stable background therapy involving 1–3 PAH drugs	Sotatercept improved exercise capacity	160
Clinical trial of upfront combination therapy that reached primary end point					
AMBITION (2015)	Ambrisentan and tadalafil in combination vs monotherapy	RCT	500 treatment-naive patients with PAH	Combination therapy significantly reduced risk of clinical failure events compared with monotherapy	134
Pivotal trials in PAH that did not result in approval of therapy in the USA or Europe					
IMPRES (2013)	Imatinib	RCT	202 patients with PAH receiving ≥2 PAH therapies	Imatinib improved exercise capacity and haemodynamics but serious adverse events and study drug discontinuations were common	150
FREEDOM-C (2012)	Treprostinil, oral	RCT	350 patients with PAH (receiving ERA and/or PDE5 inhibitor)	The primary end point of improvement in 6MWD at week 16 was not significant with treprostinil treatment	238
ALPHABET (2002)	Beraprost	RCT	130 patients with PAH	Beraprost improved exercise capacity and symptoms in patients with NYHA functional class II and class III PAH	239
Barst et al. (2003)	Beraprost	RCT	116 patients with PAH	Patients receiving beraprost showed less evidence of disease progression at 6 months but this effect was not evident at shorter or longer follow-up intervals	240

6MWD, 6-min walk distance; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase 5; PH, pulmonary hypertension; RCT, randomized, controlled trial; SC, subcutaneous.

plus tadalafil combination therapy in patients with newly diagnosed PAH (WHO functional class II and III). The initial combination treatment regimen significantly reduced the risk of the composite end point of clinical failure compared with monotherapy. Of note, this study was the first to use an expanded definition of the event-driven composite end point of 'time to clinical failure' in which 'no change' in functional class together with any worsening in walk distance was considered as a 'failure' of therapy[134]. However, the difference between the two treatment groups in the incidence of the composite end point was driven mainly by hospitalizations for PAH. Whether this added benefit of upfront combination therapy is the result of a mechanistic synergism between the two drug classes or each drug class compensating in part for unresponsiveness to the other drug class remains to be determined. In a French registry study, patients with newly diagnosed PAH who received dual combination therapy with an ERA and a PDE5 inhibitor showed improvements in WHO functional class, exercise capacity and haemodynamic indices after 4 months[135]. Furthermore, findings from two clinical trials suggested that patients receiving dual oral combination therapy with an ERA and a PDE5 inhibitor who did not meet the predefined criteria of clinical efficacy could benefit from switching from the PDE5 inhibitor to riociguat[136,137]. However, given that both trials were open-label studies, blinded and controlled studies will be needed to confirm the findings. Finally, the TRITON study[138] showed no significant difference in the primary end point of PVR between triple combination therapy (macitentan, tadalafil and selexipag) and dual combination therapy (macitentan and tadalafil) in newly diagnosed, treatment-naive patients with PAH. The latest European guidelines for the treatment of pulmonary hypertension recommend initial combination therapy for patients with PAH (idiopathic, heritable, drug-associated or connective tissue disease-associated) without cardiopulmonary comorbidities and initial oral monotherapy for those with cardiopulmonary comorbidities[5].

Importantly, PAH medications are only effective if patients can tolerate the dosing, route of administration and adverse-effect profile. The therapeutic promise of a medication might influence the ability or willingness of patients to cope with adverse effects. For example, an unfavourable side effect profile will be more acceptable for a drug with lifesaving potential and disease-modifying properties than for a less effective drug. Of note, drugs from the same drug classes can have different side effects. In a meta-analysis comparing the clinical safety of numerous ERAs, the risk of abnormal liver function was increased with bosentan treatment but not with ambrisentan or macitentan treatment[139]. With regards to prostacyclin therapies, the complications and burden of intravenous therapy will lessen with the development of subcutaneous, oral and inhaled formulations. However, combination therapy will be associated with an accumulation of adverse effects from each of the individual drugs, which might affect tolerability (Fig. 2).

Calcium channel blockers

Patients with idiopathic, heritable or drug-associated PAH who have a positive acute vasoreactivity test might benefit from treatment with a high-dose calcium channel blocker[5]. Unfortunately, the initial effectiveness of calcium channel blockers in these patients is often not sustained in the long term. In a French national registry study, 12.6% of patients with idiopathic PAH had an acute haemodynamic response to an acute vasodilator challenge but only 6.8% had a sustained response to calcium channel blocker therapy at 1 year[140]. In a multicentre, retrospective analysis of 1,904 patients with idiopathic, heritable or drug-induced PAH who underwent vasoreactivity testing, only 162 patients fulfilled

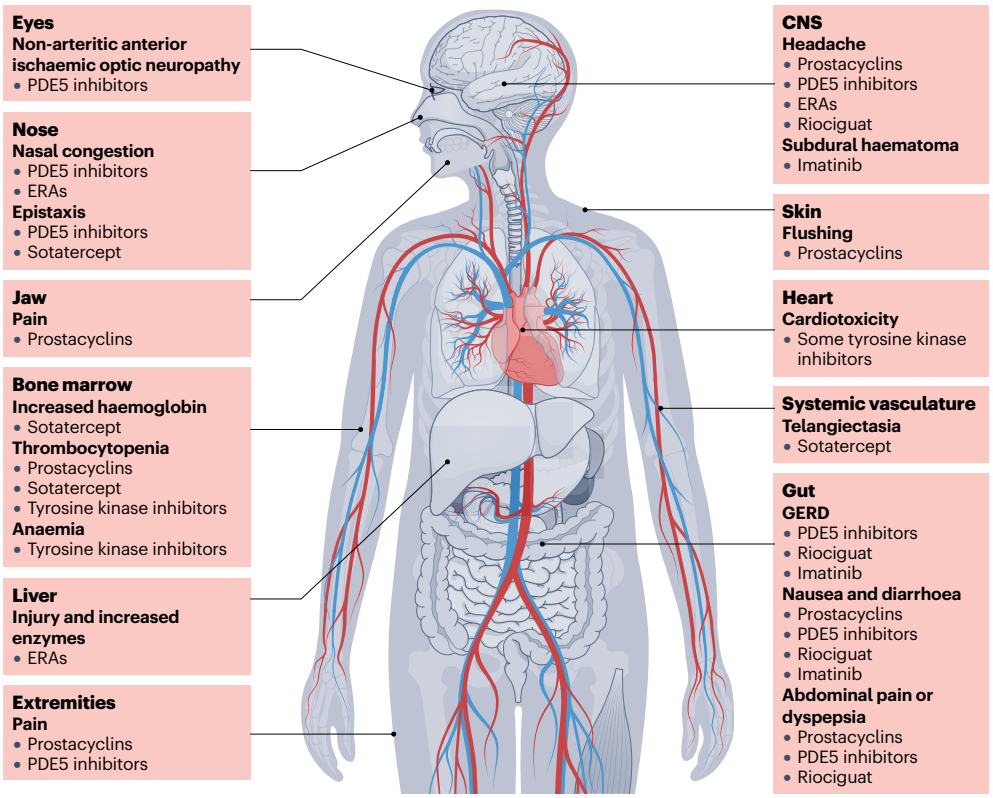

Fig. 2 | Overview of key adverse effects of approved and advanced investigative therapies for pulmonary arterial hypertension. Combination therapy will be associated with an accumulation of adverse effects from each of the individual drugs. CNS, central nervous system; ERAs, endothelin receptor antagonists; GERD, gastro-oesophageal reflux disease; PDE5, phosphodiesterase 5.

vasoresponder criteria. During a median follow-up of 60 months, overall survival was 86.7%. However, at 1 year after initiating calcium channel blocker therapy, only 53.2% of the patients remained on monotherapy with this regimen. Interestingly, in addition to the previously defined haemodynamic responder criteria, this study showed that pulmonary artery compliance during initial vasoreactivity testing, a low-risk status and low serum NT-proBNP levels during follow-up correlated with survival[141]. Therefore, patients with a positive response to a vasodilator challenge and prescribed calcium channel blockers should undergo regular reassessment with objective testing[5]. Of note, among all PAH treatments, calcium channel blocker therapy remains the only available 'personalized medicine' tool given the possibility to pre-identify probable responders.

Limitations of established therapies

The complex vascular pathobiology of PAH, which is characterized by excessive proliferation of pulmonary vascular cells, extracellular matrix deposition and perivascular inflammatory cell infiltration, poses a challenge for established treatments. The mechanism of action of established PAH therapies is predominantly limited to effects on vasodilatation through correcting the imbalance of vasoactive factors. Clinical trials evaluating these therapies have largely focused on determining their benefit on the basis of 6MWD or morbidity and mortality end points driven by disease progression or hospitalization (Table 1); no clinical trial has thus far proved which drug combinations were best for individuals or provided definitive evidence of disease modification. As such, there is a lack of evidence for physicians to predict which drug or combination of drugs will be most effective for a specific patient. A personalized medicine approach that allows for the pre-identification of likely responders (such as when prescribing calcium channel blockers) is lacking but 'big data' and omics tools might help to overcome this evidence gap in the future (see below). In addition, new strategies are needed to resolve pulmonary pathological remodelling and halt or reverse the progression of PAH. Translational and clinical research in the past decades has identified novel pathogenic pathways underpinning proliferative, metabolic and inflammatory abnormalities in PAH, providing insight into new therapeutic avenues.

Novel therapeutic targets

Imatinib

The tyrosine kinase inhibitor imatinib was the first drug of its kind to be tested in patients with PAH and opened the door to the study of new classes of drugs with pronounced anti-proliferative properties (as opposed to vasodilatory properties) to reverse vascular pathology. Imatinib is a selective inhibitor of several tyrosine kinases, including the fusion protein BCR–ABL (which promotes leukocyte proliferation), KIT and the PDGF receptor (PDGFR)[142] (Fig. 3). Imatinib was approved in 2001 for the treatment of patients with chronic myelogenous leukaemia[143]. PDGF has been shown to act as a potent mitogen and chemoattractant for smooth muscle cells and fibroblasts and is a potent inducer of smooth muscle contractile activity[144], whereas KIT is a marker of bone marrow-derived haematopoietic stem cells. Given that pulmonary vessel remodelling has been associated with upregulated PDGF activity and increased KIT expression in patients with PAH, the potential of repurposing imatinib to treat PAH has received much attention.

In animal models with established PVD, imatinib treatment was associated with robust 'reverse remodelling' effects in small pulmonary arteries, consistent with its anti-proliferative properties[145]. In a subsequent case report, the administration of oral imatinib to a patient with end-stage PAH that had progressed to right-sided heart failure despite triple therapy led to an improvement in 6MWD, PVR and WHO functional class[146]. These effects were sustained after 6 months of treatment with no apparent adverse effects[146]. After the publication of several similar case reports[147,148], a phase II, randomized, controlled, 24-week study in patients with PAH showed significantly decreased PVR and an increase (albeit non-significant) in 6MWD after treatment with imatinib compared with placebo[149]. The subsequent phase III IMPRES trial[150] showed a significant improvement in 6MWD, PVR and cardiac output in patients taking imatinib in addition to their usual PAH treatments compared with patients receiving placebo plus usual PAH treatment (Table 1). Unfortunately, adverse events (such as subdural haematoma) and study drug discontinuations were more common in the imatinib group than in the placebo group, and the FDA has requested further safety data. Nevertheless, there remains considerable interest in the use of imatinib for PAH. In a phase I trial, a dry-powder inhaled formulation of imatinib (AV-101) was well tolerated in healthy volunteers and was associated with reduced systemic exposure compared with oral imatinib[151]. An ongoing phase II–III trial in patients with PAH will evaluate the safety and efficacy of AV-101 versus placebo with a primary end point of change in PVR at 24 weeks in the phase II portion, and change in 6MWD over 24 weeks in the phase III portion[152]. Furthermore, an open-label, single-arm, phase I–II clinical study is ongoing to identify the optimal tolerated dose of oral imatinib in patients with PAH to establish its efficacy at that dose and to evaluate drug response by patient genotype[153] (Supplementary Table 1).

Seralutinib

The tyrosine kinase inhibitor seralutinib is administered via inhalation and targets PDGFRα, PDGFRβ, colony-stimulating factor 1 receptor and KIT (Fig. 3). In two rodent models of PAH, inhaled seralutinib improved cardiopulmonary haemodynamics and reduced pulmonary arterial and RV remodelling compared with vehicle treatment[154]. The phase II, randomized, double-blind, placebo-controlled TORREY trial[155] in patients with PAH receiving standard background therapy showed that inhaled seralutinib significantly reduced PVR compared with placebo at 24 weeks, meeting the primary end point of the study. Seralutinib was well tolerated, and the most common adverse event in both groups was a mild-to-moderate cough. These results suggest that drug delivery via inhalation allows sufficient activity in pulmonary circulation with a benign safety profile. An ongoing phase III trial in patients with PAH will evaluate the safety and efficacy of inhaled seralutinib versus placebo with a primary end point of change in 6MWD over 24 weeks[156] (Supplementary Table 1).

Sotatercept

Sotatercept is a first-in-class fusion protein consisting of the extracellular domain of human activin receptor type IIA (ACTRIIA) and the Fc domain of human immunoglobulin G1. Sotatercept acts as a ligand trap, sequestering members of the TGFβ superfamily to restore the balance between the pro-proliferative ACTRIIA pathway and the anti-proliferative BMPR2 pathway[157,158] (Fig. 3). Pulmonary arteriolar expression of the ACTRIIA ligands activin, growth and differentiation factor 8 (GDF8) and GDF11 was higher in patients with PAH than in healthy controls[159]. In preclinical studies, an ACTRIIA–Fc fusion protein promoted BMP9 signalling and blocked the pro-proliferative effects of GDF11 and activin in pulmonary vascular cells[159]. The ACTRIIA–Fc fusion protein also prevented and reversed PVD and RV dysfunction in two rodent models of pulmonary hypertension[159]. In a phase II, randomized,

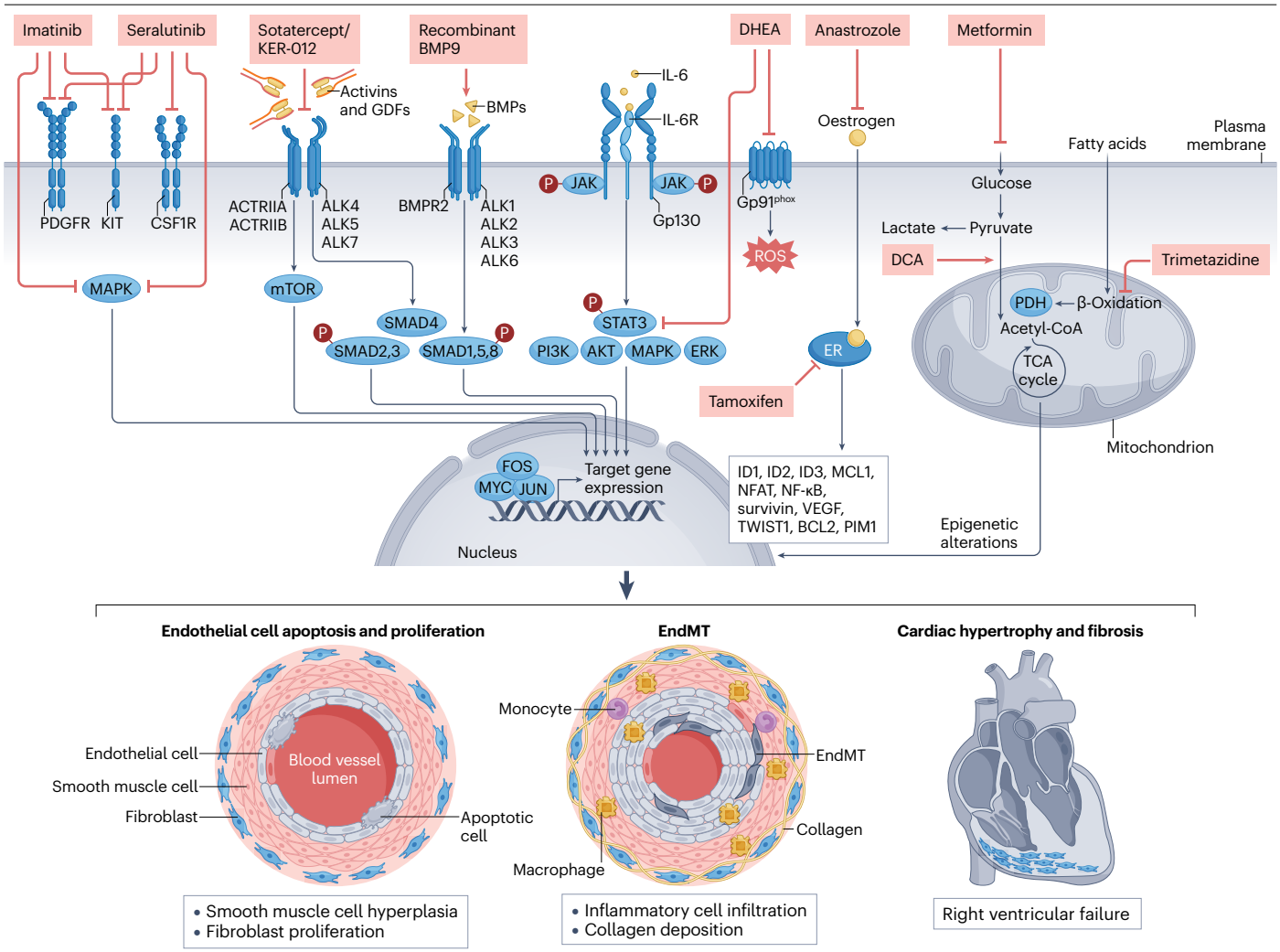

Fig. 3 | Key investigative treatment options with novel targets in pulmonary vascular disease. The tyrosine kinase inhibitor imatinib was the first predominantly non-vasodilatory drug to be tested in patients with pulmonary arterial hypertension (PAH). Inhaled formulations of imatinib and another tyrosine kinase inhibitor, seralutinib, are being evaluated in phase II and phase III clinical trials. The activin receptor type IIA (ACTRIIA) ligand trap sotatercept was approved for use in the USA in 2024; a phase II trial of the ACTRIIB ligand trap KER-012 in patients with PAH is ongoing. Sex hormone-related therapies (anastrozole, tamoxifen and dehydroepiandrosterone (DHEA)) and drugs targeting metabolism (metformin and trimetazidine) are also under investigation. Recombinant bone morphogenetic protein 9 (BMP9) is also being developed as a potential treatment for PAH, although the role of BMP9 in PAH remains inconclusive. ALK, activin receptor-like kinase; BMPR, bone morphogenetic protein receptor; CoA, coenzyme A; CSF1R, colony-stimulating factor 1 receptor; DCA, dichloroacetate; EndMT, endothelial-to-mesenchymal transition; ER, oestrogen receptor; GDFs, growth and differentiation factors; ID, DNA-binding protein inhibitor ID; IL-6R, IL-6 receptor; NF-κB, nuclear factor-κB; NFAT, nuclear factor of activated T cells; PDGFR, PDGF receptor; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; TCA, tricarboxylic acid; VEGF, vascular endothelial growth factor.

placebo-controlled trial, subcutaneous sotatercept significantly reduced PVR at 24 weeks compared with placebo in patients with PAH receiving stable background therapy[157]. The reduction in PVR with sotatercept treatment was driven by a reduction in mPAP given that there was minimal change in cardiac output[157]. In an open-label, 18–24-month extension phase of this trial in which all participants received sotatercept, efficacy end points were improved in patients who switched from placebo to sotatercept at the start of the extension phase and were maintained in the original sotatercept group[158]. Finally, in a phase III randomized trial, subcutaneous sotatercept was compared with placebo in patients with PAH receiving stable background therapy[160] (Table 1). The majority of patients (61.6%) were receiving background triple therapy. The sotatercept group showed a significant improvement in 6MWD (the primary end point) compared with the placebo group as well as a significant improvement in secondary end points, including PVR, plasma NT-proBNP level, WHO functional class, time to death or clinical worsening, French risk score, and patient-reported outcomes. As in the phase II trial, minimal change was observed in cardiac output.

Although the efficacy data are impressive, emerging safety signals warrant discussion. In the phase II trial, thrombocytopenia and haemoglobin levels were increased in the sotatercept group but not in the placebo group, as expected[157]. In the long-term extension of the

phase II trial, telangiectasia was also reported as an adverse event in 11 participants (10.6%)[158]. In the phase III trial, minor bleeding episodes, epistaxis, gingival bleeding, dizziness and an increase in blood pressure occurred more frequently with sotatercept treatment than with placebo[160]. Although dangerous arteriovenous malformations have not been reported in patients receiving sotatercept, reports of telangiectasia suggest an off-target systemic vascular effect that warrants further investigation. Of note, variants in ALK1 have been implicated in PAH that is associated with hereditary haemorrhagic telangiectasia[9]. The lack of beneficial change in cardiac output in patients receiving sotatercept, despite improvements in PVR and mPAP, is also unexpected and might be of concern given that preclinical data suggest that sotatercept-like drugs might have detrimental effects on the heart[161]. Of note, however, the study participants were receiving established PAH therapies and had a normal cardiac index at baseline, which might partly explain the absence of further increments in cardiac index. The long-term implications of the safety findings remain to be established. An open-label follow-up study is ongoing in patients with PAH to assess the longer-term safety, tolerability and efficacy of sotatercept[162]. Furthermore, two other phase III trials are currently evaluating sotatercept in patients with PAH (WHO functional classes III or IV) at high risk of death[163] and in patients with newly diagnosed PAH at intermediate or high risk of disease progression[164] (Supplementary Table 1).

Recombinant BMP9

Variants in *BMP9* have been associated with PAH, and some patients have decreased *BMP9* expression even in the absence of these variants[165]. MGX292, a recombinant variant of *BMP9* that is associated with reduced osteogenic activity and similar endothelial signalling activity compared with native *BMP9*, reversed pulmonary vascular remodelling in a rat model of severe obliterative PAH and is being developed as a potential treatment for PAH[166]. However, the role of BMP9 as a therapeutic target in PAH is controversial. Administration of BMP9 has been shown to reverse PVD in rodent models of severe obliterative PAH[167] and to attenuate PVD characteristics in a rodent model of PVD with pulmonary fibrosis[168]. Conversely, however, other studies showed that deletion or inhibition of BMP9 reduced PVD[169,170]. These findings can be explained by the association of variants in the genes encoding the BMP9 receptor ALK1 and the co-receptor endoglin with hereditary haemorrhagic telangiectasia; deletion or inhibition of BMP9 could potentially lead to vasodilatation reminiscent of that observed in haemorrhagic telangiectasia, which could protect against the development of PVD[171]. Further confusing its role in PVD, cell type-specific genetic inactivation of BMP9 and BMP10 in mice has been shown to attenuate vascular smooth muscle cell contractility and decrease blood pressure[172]. By contrast, overexpression of BMP10 increased vascular contractility and blood pressure. Overall, in light of the mixed preclinical and clinical data, the role of BMP9 in PAH remains inconclusive[173].

Sex hormone-related therapies

Studies in animal models of pulmonary hypertension have reported discrepant effects of oestradiol on the pulmonary vasculature but this hormone has been shown to have a protective effect on RV function and adaptation[52]. In two rodent models of pulmonary hypertension, inhibition of oestradiol synthesis with the aromatase inhibitor anastrozole attenuated the development of PVD but only in female rodents[174]. In a small proof-of-principle randomized controlled trial in men and post-menopausal women with PAH receiving stable background therapy, anastrozole was well tolerated and increased 6MWD compared with placebo, although no improvements were observed in RV parameters (assessed by echocardiography), circulating biomarkers, functional class or health-related quality of life[175]. The results from a larger randomized, controlled phase II trial with a similar patient cohort are awaited[176].

The role of the oestrogen receptor antagonist tamoxifen in PAH has also been explored. In a preclinical model of heritable PAH (mice with a mutation in *Bmpr2*), tamoxifen partially reversed PVD[177]. Although more robust inhibition of oestrogen using a combination of anastrozole and fulvestrant seemed to be more effective for the treatment of PAH in the mouse model, tamoxifen might be more useful in pre-menopausal women with PAH given the lower risk of inducing menopause. The results of a small, randomized, controlled phase II clinical trial of tamoxifen in men and women (both pre-menopausal and post-menopausal) with PAH receiving stable background therapy are awaited[178].

Finally, DHEA, a precursor for oestrogen and testosterone, has been shown to reduce pulmonary vascular remodelling in rat models of severe obliterative PAH[179] and other forms of PVD[180–182]. In an uncontrolled pilot trial evaluating the efficacy of DHEA in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease, DHEA treatment was associated with improvements in 6MWD and pulmonary haemodynamics from baseline and no evidence of worsening of gas exchange[183]. A phase II trial assessing the effects of DHEA in patients with PAH on stable background therapy is ongoing[184,185] (Supplementary Table 1).

Metabolism

PAH has been linked with metabolic dysfunction[2], and the antidiabetic drug metformin has been shown to be protective against PAH, possibly owing to its vasodilatory and anti-proliferative properties[186]. Metformin protected against pulmonary vascular remodelling in rat models of pulmonary hypertension (induced by hypoxia or monocrotaline)[186] and in female but not in male rats with severe obliterative PAH (induced by hypoxia combined with SU5416, an inhibitor of vascular endothelial growth factor receptors 1 and 2)[187,188]. In a randomized, controlled pilot trial, metformin and bosentan combination therapy improved 6MWD and PVR index to a greater extent than bosentan monotherapy in patients with PAH associated with congenital heart defects[189]. A phase II, randomized, controlled trial evaluating metformin treatment in patients with PAH receiving stable background therapy is ongoing[190] (Supplementary Table 1).

The role of the Warburg effect — the shift of cellular metabolism from glucose oxidation to glycolysis despite the presence of oxygen — in the development of PAH could also be targeted. Dichloroacetate promotes glucose oxidation by inhibiting pyruvate dehydrogenase kinase (Fig. 3). In rodent models of PVD, dichloroacetate prevented and reversed the disease by restoring the expression and function of voltage-gated potassium channels[191], decreasing pulmonary arterial cell proliferation and promoting apoptosis[192,193]. RV function was improved through regression of PVD and through direct effects of dichloroacetate on the right ventricle[115,194]. In a rat model of severe obliterative PAH, dichloroacetate prevented but did not reverse the formation of neointimal lesions[195]. Patients with idiopathic PAH receiving open-label treatment with dichloroacetate for 4 months showed overall improvements in mPAP, PVR and functional capacity from baseline but a subset of patients with loss-of-function polymorphisms in sirtuin 3 and uncoupling protein 2 had no response and dose-limiting toxicity (grade 2 peripheral neuropathy) developed in the patients receiving the highest dose[196]. Given this dose-limiting risk of neuropathy

and considerable inter-individual variations in drug metabolism[197], dichloroacetate might not be an ideal therapeutic candidate for PAH. Nevertheless, these study findings show the feasibility of targeting cellular metabolic alterations in PAH and the importance of individualized therapy. Glucose oxidation might also be promoted indirectly via activation of the Randle cycle by using a fatty acid oxidation inhibitor such as trimetazidine[198]. In rats with pulmonary artery banding, trimetazidine prevented the development of RV hypertrophy and improved cardiac index and exercise performance compared with placebo[199]. A phase II, randomized, controlled pilot trial in patients with PAH showed a small but significant improvement in RV remodelling and a significant increase in 6MWD with trimetazidine compared with placebo[200].

The serotonin pathway

Plasma serotonin levels are increased in patients with PAH compared with healthy volunteers[201] and anorexigens such as fenfluramine (which increases the availability of serotonin) are associated with an increased risk of PAH[202]. However, a signalling pathway that is altered in a disease is not necessarily an appropriate target for the treatment of that disease. Various agents targeting the serotonin pathway (including receptor antagonists, receptor agonists and transporter reuptake inhibitors) have been investigated as potential therapies for PAH but were unsuccessful in clinical trials[203]. A phase IIb study of the tryptophan hydroxylase inhibitor rodatristat ethyl (which targets serotonin biosynthesis) in patients with PAH did not meet its primary end point of change in PVR at 24 weeks[204,205]. Based on these early study results, including an analysis of the safety data, the ongoing studies of rodatristat ethyl have been discontinued[204].

Outlook and unmet medical needs

Deep phenotyping

Deep phenotyping, which involves the integration of detailed clinical information with molecular information (including genomic, proteomic and metabolomic data), will improve our understanding of PAH and has the potential to advance the management of this complex disease. Proteomic analyses have revealed the differential expression of numerous proteins in the lungs of patients with PAH compared with individuals without PAH[206] and identified prognostic markers in plasma from patients with PAH[207,208]. Exome or whole-genome sequencing and genotyping array data have also uncovered novel, rare and common genetic variants associated with PAH[209–212], and metabolomics analyses demonstrated a link between metabolic profiles and survival in patients with idiopathic or heritable PAH[60].

Future applications for deep phenotyping PAH research include the identification of signatures of diagnostic value, assessment of risk, identification of novel therapeutic targets, prediction of response to treatment and monitoring of drug effectiveness. For example, plasma NT-proBNP levels have a high sensitivity but low specificity for the diagnosis of PAH and other single biomarkers have not been clinically validated[213]. Deep phenotyping might facilitate the discovery of panels of biomarkers with increased specificity. Whole-blood RNA sequencing led to the identification of a panel of 25 RNAs that distinguished patients with PAH from healthy controls with 87% accuracy and was associated with disease severity and long-term survival[214]. Unsupervised machine learning has also been used to identify groups with poor, moderate or good prognosis on the basis of a combination of whole-blood transcriptomic and clinical signatures in patients with idiopathic PAH[215]. A combination of clinical and omic analyses is also being used in the PVDOMICS initiative launched by the National Heart, Lung and Blood Institute[216]. Findings from this project indicate that a substantial proportion of patients with pulmonary hypertension have more than one type of the condition according to the current classification, and one of the aims of the initiative is to update the classification of PVD based on deep phenotyping data[1]. Finally, the Pulmonary Vascular Research Initiative GoDeep meta-registry is currently collecting deep phenotyping data from pulmonary hypertension centres worldwide using a common clinical parameter set of >350 items[217].

Predicting response to treatment

The current approach to testing the efficacy of PAH treatment[5] might provide a positive average treatment response across a group of patients but individual responses might vary[218]. To improve the benefit–risk balance of PAH therapy and optimize outcomes for individual patients, a personalized medicine approach is needed. Research is ongoing to identify biomarkers that will help to predict individual responses to treatment. For example, high endothelin 1 levels in blood samples were found to be associated with a subsequent decline in 6MWD in patients with PAH receiving an ERA, a PDE5 inhibitor or both[219]. Of note, in the patients receiving ERA monotherapy, high levels of asymmetric dimethylarginine (ADMA) were associated with low 6MWD. Given that ADMA blocks nitric oxide synthesis[220], PDE5 inhibition might potentially compensate for this effect. Among patients receiving ERAs, ADMA levels might thus help identify those who are likely to benefit from initiating PDE5 inhibitor treatment. Furthermore, the serum levels of activin A and follistatin-like 3 have been identified as prognostic biomarkers in patients with PAH[221], but whether serum levels of these proteins can also predict response to treatment with activin receptor ligand traps requires further research. A genome-wide association study identified polymorphisms in the endothelin 1 pathway that were associated with ERA efficacy[222], and RNA expression profiling in cultured lymphocytes was used to identify patients with PAH who responded to calcium channel blocker therapy[223]. The utility of these approaches for predicting treatment response requires further validation.

RV function

Although the primary disorder in PAH is in the pulmonary vasculature rather than in the right ventricle (which almost always recovers after lung transplantation[224]), RV function has a crucial role in determining patient outcomes[4]. However, our understanding of the mechanisms involved in RV function and failure in PAH is incomplete[4]. The adaptation of RV contractility to afterload (that is, RV–pulmonary arterial coupling) is defined as the ratio of end-systolic elastance to arterial elastance[225]. RV–pulmonary arterial coupling has considerable reserve, decreasing from normal values of 1.5–2.0 to <0.7 before uncoupling occurs[225].

PAH treatment can lead to the recovery of load-dependent RV function, but the direct effects of PAH drugs on load-independent RV function have not yet been sufficiently investigated. Preclinical evidence suggests that some of these drugs have direct detrimental effects on the RV myocardium. For example, ERAs were found to decrease contractility in hypertrophied but not in healthy right ventricles in ex vivo modified Langendorff perfusions[226]. Furthermore, in rats and in patients, the expression of endothelin type A receptor and endothelin1 was increased in hypertrophied versus normal right ventricles, possibly as a compensatory mechanism to preserve contractility in the presence of increasing afterload[226]. An ongoing open-label pilot trial aims to evaluate the effect of the ERA macitentan (as well as the sGC

stimulator riociguat in a separate treatment group) on load-independent contractility and RV–pulmonary arterial coupling in patients with PAH[227].

The effect of prostacyclins on contractility in patients with PAH has been assessed in two clinical studies, with mixed results. Inhalation of a single dose of iloprost acutely increased RV contractility (end-systolic elastance) and decreased afterload (arterial elastance) from baseline[228], whereas subcutaneous administration of treprostinil for 3 months led to a decrease in end-systolic elastance and arterial elastance from baseline, with preserved RV–pulmonary arterial coupling[229].

The effect of PDE5 inhibition on contractility also remains unclear. PDE5 inhibition increased contractility in the myocardium of rats with RV hypertrophy[230]. However, sildenafil had no acute effect on estimates of contractility in patients with advanced heart failure with reduced ejection fraction[231] or in patients with heart failure with preserved ejection fraction[232].

Finally, sotatercept-like drugs might be a double-edged sword, with beneficial effects in pulmonary circulation but detrimental effects in the heart. In a zebrafish model, suppression of the ACTRIIA signalling pathway (through a loss-of-function mutation in activin-βA) interfered with cardiac repair mechanisms and cardiomyocyte proliferation[161]. Interestingly, increased ACTRIIB signalling (through overexpression of myostatin B) also had a detrimental effect on the myocardium[161]. Drugs that suppress ACTRIIB signalling might thus provide greater benefit than drugs that target ACTRIIA. The ACTRIIB ligand trap luspatercept is approved for use in transfusion-dependent patients with β-thalassaemia and patients with myelodysplastic syndromes with ringed sideroblasts at very low-to-intermediate risk of acute myeloid leukaemia or death (according to the Revised International Prognostic Scoring System[233]) who did not respond to, or are ineligible for, an erythropoiesis-stimulating agent[234]. Given that luspatercept-like drugs might mediate beneficial effects on pulmonary circulation without adversely affecting the heart, investigating their potential efficacy in treating PAH is of great interest. The investigational ACTRIIB ligand trap KER-012 has shown promising preclinical results, preventing pulmonary vascular remodelling and RV fibrosis in a rat model of PAH[235]. In a phase I trial in healthy women in post-menopause, KER-012 was well tolerated and reduced plasma NT-proBNP levels[236]. A phase II trial in patients with PAH is now in the recruitment stage and will evaluate the safety and efficacy of KER-012 versus placebo, with a primary end point of change in PVR over 24 weeks[237].

Conclusions

Although much progress has been made in the management of PAH, substantial challenges remain. The development and FDA approval of sotatercept — the first PAH drug to target a new signalling pathway since the approval of sildenafil in 2005 — is a pivotal step in the evolution of PAH treatment. Issues with long-term safety, polypharmacy and socioeconomic disparities in treatment availability need to be addressed to improve patient outcomes and reduce disease burden. Research on the mechanisms of RV dysfunction and the adaptation of RV function to an increase in afterload might contribute to further advances in PAH management. Furthermore, the current pulmonary hypertension classification system might need to be revised to account for intermediate or overlapping disease subtypes. In the future, deep phenotyping is expected to have a growing role in the classification of pulmonary hypertension, PAH diagnosis and risk assessment, identification of novel therapeutic targets, and the development of a personalized medicine approach.

Published online: 07 August 2024

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Acknowledgements
H.-A.G. has received research funds from the German Research Foundation (DFG; CRC 1213 projects B08 and A09), the Cardiopulmonary Institute (CPI), the Institute for Lung Health (ILH) and the German Center for Lung Research (DZL). L.Z. has received research funds from the British Heart Foundation (PG/19/17/34275, RE/18/4/34215), DFG (CRC 1213 project B08), the CPI, the ILH and the DZL. F.G. has received research funds from public sources from the DFG (CRC 1213 project A08), the CPI, the ILH and the DZL.

Author contributions
All authors contributed to all aspects of this manuscript.

Competing interests
H.-A.G. has received fees for lectures and/or consultations from Aerovate, Altavant/Enzyvant, Bayer AG, Gossamer Bio, Janssen/Actelion, MorphogenIX, MSD/Acceleron, Pfizer, and United Therapeutics and fees for participation in a data safety monitoring board from Insmed. His spouse was an employee of Altavant/Enzyvant from January 2023 until August 2023; her work for the company was intentionally separated from H.-A.G.'s active interactions in conjunction with the clinical development programme. M.G.-M. has received research grants paid to her institution from Aerovate, Altavant, Acceleron (a subsidiary of Merck), and Bayer and consultation fees from Aerami, Acceleron (a subsidiary of Merck), Bayer, Janssen Biotech, Keros Therapeutics, and United Therapeutics Corporation. She holds leadership roles on the Board of Directors for the International Society of Heart and Lung Transplantation and the Scientific Advisory Board of United Therapeutics. Her spouse is a Senior Director in Clinical Development at Intellia Therapeutics. The other authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41569-024-01064-4.

Peer review information *Nature Reviews Cardiology* thanks the anonymous reviewers for their contribution to the peer review of this work.

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